Section 4)

Attachment no. 4

C.R.F. S.p.A.:

Teratology report on Fructose-1,6-Diphosphate,

1977

CRF centro ricerca farmaceutica
s.p.a.

4

NON CLINICAL LABORATORY INSPECTION DATA

OF THE STUDY CRF 023

Dr. ALFREDO NUNZIATA

DIRECTOR OF CRF

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CAPITALE SOCIALE LIRE 1 000 000.000 - C.C.I.A. N 375736 - REG. SOC. TRIB. DI ROMA

CRF-023

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TERATOGENISIS REPORT ON ESAFOSFINA PRODUCED BY BIOMEDICA FOSCAMA CO. OF ROME

CODE C R F - 0 2 3

TERATOLOGY IN NEW ZEELAND RABBIT

One daily i.v. administration (from the 6th to the 18th day of pregnancy).

PRELIMINARY DATA

The compound, ESAFOSFINA, produced by the Biomedica Foscama Co., for which a teratological study was carried, is classified in our books under the code CRF 023.

The analytical data are reported in the attached analysis certificate. Certificate no. 10478 corresponds to production lot no. 2 of January 22, 1976, the same of the substance tested by us in the teratological trials described hereafter.

A 20 g sample of the substance is in our archives, under the code CRF 023, and is available for control.

The following material and documents are also in our archives under the same code :

1) original books and clinical card,
2) copy of the report
3) fetuses stained with alizarine for skeletal malformations
4) fetuses fixed in formaldehyde and embedded to discover internal malformation.

The material will be kept for 5 years from the date of this report.

A) EXPERIMETANL PROTOCOL

PURPOSE

To determine whether the product under examination, when it is injected intravenously, induces malformations during pregnancy. The two doses are selected so that the higher is close to the toxic level while the lower is a multiple of the daily curative dose and precisely :

Dose I	200 mg/Kg i.v.
Dose II	100 mg/Kg i.v.
Dose III	apyrogenic saline

The doses were injected in volumes of 4 ml/Kg. The solutions were prepared by dissolving 5 g of ESAFOSFINA in 25 ml of bidistilled water which are brought to 100 ml for Dose I and to 200 ml for Dose II with sterile apyrogenic saline. The solutions are injected slowly (2 ml/minute) in the marginal veins of both ears.

B) EXPERIMENTAL CONDITIONS

36 female New Zeeland rabbits (body weight 2500 g) kept in standard conditions in individual cages were controlled daily for appearance of estrus (congested vulva). When it appeared the animals were mated and from the 6th to the 18th day of pregnancy, they are treated with the selected doses of the test substance. Pregnancy proceeded. On the 30th day of pregnancy, the animals were sacrificed and the fetuses examined after caeserean section. The number of live, dead, reabsorbed fetuses, their weight, sex, the number of nidations, left and right corpus leuteum were noted and analyzed. The presence of macroscopic malformations was recorded. One third of the fetuses was fixed in Bouin to study vwas malformations, the other two thirds is treated so that skeletal malformations might be evidenced.

C) EXPERIMENTAL PROCEDURE

36 sexually mature female New Zeeland virgin rabbits (body weight 2300-2800 g), kept in single cages under standard conditions (22° C

temperature, 50-55% relative humidity), nourished with a Mil Morini Rabbit Feed and water ad libitum, were used for the experiment. The animals were randomly mated to healthy males on the first day of estrus. Copulation day was considered zero day of gestation. The rabbits were under observation daily and their body weight and diet consumption were controlled every 5 days until the 30th day of gestation.

The substance tested was administered from the 6th to the 18th day of pregnancy.

Group I	200 mg/Kg i.v.
Group II	100 mg/Kg i.v.
Group III	sterile apyrogenic saline

The rabbits were sacrificed on the 30th day with an intrahepatic injection of TANAX.

The uterus was opened and the number of nidations and fetuses recorded. Eventual external malfromations, the sex and weight of the fetuses was also registered. The number of nidations, live and dead fetuses, reabsorbtions, miscarriages, corpus leutum of the right and left ovaries, were annoted.

The fetuses were than sacrificed: 2/3 were dissected to eliminate visceral abnormalities and stained with red alizane S to show eventual skeletal malformations; the remaining 1/3 was fixed in solution to study the visceral tissues.

D) STATISTICAL ANALYSIS

Body weight increase and diet consumption of the pregnant rabbits

were analyzed statistically. The nidations, the number of fetuses - live, dead, male, female - the relative body weight were averaged and a variance analysis of the average values between the groups and between the group and control are carried out.

The number of dead and reabsorbed fetuses and miscarriages in the groups and controls was processed statistically with the x^2 method, as corrected by Yates.

A. L. Delaunois, Biostatistics in Pharmacology, Vol. II, 907, New York, Pergamon Press, 1973

Snedecor and Cochran, Statistical Methods, IV ed., Iowa State University Press, 218, 1967

E) RESULTS

None of the animals died during the test. The pregnant females' weight increase was constant for both treated and control animals (Figure 1). Diet consumption for each group, indicated in Figure 2, shows lower levels for the higher concentration group.

The following information was recorded when the animals were sacrificed :

nidations	females
fetuses	corpus leutum on right ovary
live fetuses	corpus leutum on left ovary
dead fetuses	weight male fetuses
reabsoptions	weight female fetuses
miscarriages	total average weight of fetuses
male	

Among the animals treated with Dose I (200 mg/Kg i.v.) there were 5 cases of reabsoptions in 3 females and 3 miscarriages. In those treated with Dose II (100 mg/Kg i.v.), there was 1 case of uterine reabsorption and 5 miscarriages. Group III, the controls, had 4 cases of reabsorptions in 1 female and 3 miscarriages.

Analysis of overall results reveals that there is no difference in the parameters involved in the teratological test, i.e., the number of reabsorptions, dead births and miscarriages: none of these three parameters have significance for the X^2 function.

Also the number of fetus nidations and live births , between the groups, was not significant.

The weight of the fetuses of the animals on the higher dose was significantly lower than that of the controls, although not correlated to the dose.

F) FETAL ABNORMALITIES

Examination of the fetuses (see Table) did not reveal a larger number of abnormalities that may be attributable to treatment of the pregnant rabbits with ESAFOSFINA.

Furthermore, skeletal malformations were randomly distributed and in no way correlated to the dose.

The cases of smaller fetuses, without skeletal malformations, were distributed randomly between control and treated animals.

G) CONCLUSIONS AND COMMENTS

The teratologic study conducted on ESAFOSFINA, produced by the Biomedica Foscama Co. of Rome, showed that pregnant rabbits did not suffer effects of any nature, demonstrating that the doses administered were well tolerated.

The low number of reaborptions and miscarriages, as well as the careful examination of the fetuses, shows, moreover, that ESAFOSFINA, at the doses employed in our experimental conditions, is neither enthryo-toxic nor teratogenetic.

Pomezia, September 20, 1977

CRF centro ricerca farmaceutica
s.p.a.

STATEMENT OF C.R.F.

The toxicological study of CRF 023: Esafosfina[R] - Teratological study in New Zealand rabbit has been performed by our Centre from 4/1/1977 to 20/9/1977.

The researchers of various departments are:

TOXICOLOGY

Piero Mercatelli (B.Sc.)

HISTOPATHOLOGY

Alberta Argentino-Storino (B.Sc.)

BIOCHEMISTRY

Renato Ottavio Salerno (B.S.)

TECHNICAL DIRECTOR - MINISTERIAL EXPERT

Alfredo Nunziata (PHD)

SCIENTIFIC DIRECTOR

Giulio Cesare Perri (MD. PHD.)

The "Curricula Vitorum" of the above-mentioned are enclosed.
All the original documents, the specimen, the slides and all the material concerning this experiment are available for inspection in our own files at the following address:
C.R.F. S.p.A. - Via TIto Speri, 14 - Pomezia - Rome - Italy.

...ica S.p.A.
...Alfredo Nunziata

STUDY C.R.F. O.23: TERATOLOGY ON RABBIT (1977)

File: It contains the protocol with the note regarding the choice of the doses.

Row data: Drafts of cards and tables with row data collected during the experiment.
Out put of the computer and apparatus used for data analysis.
Out put apparatus are dated and signed.

Roma, 15.5.1982

R. Costnini

Mr. A. Lupi	: Toxicology worker
Mr. M. Paciarotti	: " "
Mr. V. Delfino	: " "
Mrs. A. D'Antona	: Histopathology worker
Dr. M. Monaco	: Mutagenetist
Dr. V. Ortali	: " "
Mrs. A. Dello Russo	: Mutagenesis worker
Mrs. T. Brustolin	: " "
Mrs. I. Di Filippo	: " "
Mrs. M. Tranquille	: Scientific Secretary

2. Employees practice good sanitation amd health habits.

   Yes in respect of Italian laws.

3. Employees follow standard operating procedures for health and safety and have adeouate laboratory clothing appropriate for their duties and to prevent microbiological or chemical contamination of the test substance.

   Yes in respect of District Regulations. Such operating procedures are not written.

4. All employees are instructed to report to supervisory personnel any and all health or medical conditions that may be considered to adversely effect the study.

   Yes at the moment of the agreement amd periodically depending from the type of protocols.

C. QUALITY ASSURANCE UNIT

1. There is a quality assurance unit (QAU).

   QAU in Italy in 1976 was called Responsible of Ministry of Health and he was Dr. Alfredo Nunziata.

2. A master schedule sheet of all nonclinical laboratory studies is maintained by the QAU.

   Schedule sheet was maintained in a central file.

3. Copies of all protocols and standard operating procedures are maintained by the QAU.

   Yes

4. Critical reviews of final reports are made to assure accuracy of description with respect to methods,; and,

   Yes critical reviews of final reports were made by the Scientific Director and Responsible of Ministry of Health.

5. Standard operating procedures;and,

   Critical reviews were made by people in C4 using all materials.

6. Observations; and,

   Critical reviews were made by people in C4 using all materials.

7. Raw data; and,

   Critical reviews were made by people in C4 using all materials.

8. Results (assuring that all adverse findings are indeed included in the final report)

   Critical reviews were made by people in C4 using all materials.

9. Procedures are written that describe the responsibilities of the QAU and the records it maintains.

   Responsibilities of the QAU (Responsible for Ministry of Health) are written in Italian Ministry of Health Circular 54 bis and 75.

D. EQUIPMENT

1. Equipment of appropriate design and adequate capacity is available to obtain values reported.

   Yes.

2. Location of equipment permits easy operation, cleaning and maintenance; and,

   Yes.

3. Is cleaned, inspected and maintained regularly.

   Yes.

4. There are written standard operating procedures which describe in detail the methods, materials and schedules to be used in the routine inspection, cleaning, maintenance, testing and calibration of equipment; and,

   Procedures for equipment in respect of the procedures of the suppliers for cleaning etc. are not written procedures but only internal regulations and control of Head of Laboratory.

5. The specific remedial actions to be taken in the event of failure or malfunction of equipment;and,

   Yes.

6. Designates the individual responsible for each of the operations.

   Yes for each laboratory the Head is the individual responsible.

7. Copies of the standard operating procedures are available to laboratory personnel.

   References of the methods and procedures are available to laboratory personnel.

E. TESTING FACILITY OPERATION

1. Separate laboratory space is provided for the performance of routine procedures or categories of procedures; and,

   Yes.

2. Separate laboratory space is provided for the performance of specialized activities such as aseptic surgery, intensive care, necropsy and radiography

   Yes.

3. Spaces of cleaning, sterilizing, and maintaining equipment and supplies used during the course of the study are separate from the areas housing the test system.

   Yes.

4. Studies involving radioactive or other biohazardous materials are carried out in special facilities or areas which provide protection to personnel, test systems, and the external environment against contamination or unnecessary radiation exposure, or infection.

   Yes.

5. Persons possessing and using radioactive materials are licensed in accordance with the Nuclear Regulatory Commission regulations or meet the requirements of an agreement state.

   Yes.

6. Special procedures are employed for the handling of other biohazardous materials.

   Yes in respect of the Italian laws.

7. Written standard operating procedures (which at least meet GLP requirements) are maintained detailing the methods to be used in performing nonclinical laboratory studies.

   No. Detailed methods were written or photocopy of references was made available.

8. Standard operating procedures are established for animal room preparation; and,

   Idem as E7.

9. Animal care; and,

   Idem as E8.

10. Test and control substances, receipt, identification, strength, quality, purity, stability, storage, handling, mixing, sampling and administration; and,

    In respect of the Italian regulations.

    A sample of the test article is being kept in the archives.

11. Test system observations; and,

    Idem as E7.

12. Laboratory test; and,

    Idem as E7.

13. Handling of animals found moribund or dead during study; and,

    Idem as E7.

14. Necropsy of animals or post-mortem examination or animals; and,

    Idem as E7.

15. Preparation of specimens; and,

    Idem as E7.

16. Histopathology; and,

    Idem as E7.

17. Data handling, storage, and retrieval; and,

    Idem as E10.

18. Preparation and validation of final study report.

    Idem as E10.

19. A historical file of standard operating procedures annotating effective dates and dates of revisions is maintained.

    No data are only available for all materials of the study that are kept in the archives or in a general file.

20. The relevant standard operating procedures are available at all times in the immediate bench area of personnel performing the procedures.

    Idem as E19.

21. All reagents and solutions in the laboratory area are labeled adequately.

    In respect with Italian regulations.

F. ANIMAL CARE

1. The testing facilities which utilize cats, dogs, guinea pigs, hamsters, rabbits, or nonhuman primates have been inspected by the U.S. Department of Agriculture Animals Plant Health Inspection Service, and found to be in compliance with the Animal Welfare Act of 1970 (9CFX Part 3) within the past 2 years (Indicate date and results; and/or

   Not only by the Italian Ministry of Health

   Physician of the Province

   Veterinary of the Province

   ENPI

   Ispettorato del lavoro

2. Feed and water used for animals are analysed periodically for the presence of known interfering contaminants.

   Suppliers certified the quality of water (District Administrat and that of food (Morini S. Polo d'Enza - Italy).

3. A program for adequate veterinary care and humane treatment h been established and is supervisied by a doctor of veterinary dicine (INdicate name of DVM) for studies involving cats, dog guinea pigs, hamsters, rabbits, or nonhuman primates; and,

   Veterinary care was made in respect of Italian regulations by Dr. P. Mercatelli and supervised by the Province and District Veterinary.

4. For studies involving other animals by either a doctor of vet nary medicine of by other qualified persons (indicate name ar qualifications).

   Idem as F3.

5. Animals either known to be, or suspected of being diseased, carriers of a disease, are isolated in an area contiguous wi or near the animal housing area.

   Yes.

6. Animals are free of any naturally occuring diseases or conditions that might interfere with the purpose or conduct of the study.

   Yes.

7. The diagnosis, authorization for and description of the treatment (including dates of treatment of animals involved) of test systems is adequately documented.

   Only if it happens, without written authorization.

8. Methods for the unique and permanent identification of all animals when needed have been developed and applied to preclude mixup of animals and/or their tissues; and,

   Yes.

9. Routine of specialized housing of animals of different species or of the same species used for different studies is adequate to preclude interspecies transmission of infection, mixup, or other events that may affect the outcome of a study or studies

   Yes.

10. The proper placement of animals which are transferred from one cage to another in the same location is checked by the transfe rer and verified by a responsible person appropriately documen ted, and a record of the procedure maintained.

    No.

12. Animal waste and refuse is collected, stored and disposed of i a safe and sanitary manner so as to preclude vermin infestatic odors, and disease hazards.

    Yes.

13. Animal cages, racks and accessory equipment are cleaned and s nitized at appropriate intervals as recommended in HEW Public tion No. (NIH) 74-23 or subsequent revisions.

    Yes.

14. Storage areas for feed, bedding, suppliers, clean cages, and equipment are separate from areas housing the test systems as well as the quarantine and isolation area, and these materials are protected against spoilage, infestation or contamination.

Yes.

G. TEST AND CONTROL SUBSTANCES

1. Each container for a test and control substance is appropriatel labeled and adequately stored to maintain the identity, strengt quality, and purity of said substances.

   It was labeled by the Sponsor and stored in cold room.

2. An appropriately identified reserve sample selected at random from each batch of test and control substance used in a study of more than 4 weeks duration, is taken, stored in an identica immediate container under appropriate storage conditions, and analyzed at the time the batch is depleted, at the termination of the study, or at the expiration date (whichever occurs firs to assure that the identity, quality, strength, purity, and st bility conform to established specifications.

   No.

3. If test or control substances are mixed with a carrier prior t administration each batch of such mixture is tested periodical for the adequacy of the mix to assure uniformity and to deter- mine the concentration of the substance in the mixture. Descr procedures used.

   No only at the beginning by the Sponsor.

4. Enough samples of each batch of the mixture are returned to th Sponsor for such analysis if the study is a blind study.

   No.

5. Each batch of the test and control substance-carrier mix is t for stability for at least the length of time between mixing use and to establish storage conditions and an expiration dat

   No.

6. For each batch of the test and control substance, tests are p formed to determine the release from the carrier mix and the

7. For each batch of test and control substance mixed with a carrier an appropriately identified reserve sample of each batch of the substance-mixture is taken and retained for the required length of time.

   No.

8. All handling, storage and disposal of known or suspected chemical carcinogens used as the test substance in a study are treated in accordance with the safety principles set forth in the "National Cancer Institute Safety Stamdards for Research involving Chemical Carcinogens", HEW Pub. No. (NIH) 75-900.

   Yes in respect of Italian regulations.

H. STUDY IMPLEMENTATIONS AND CONDUCT

1. Scientists or other professional persons are available to provide assistance and consultation to subordinates and to handle unforseen issues.

   Yes.

2. Specimens are identified by test system number, study number, nature of specimen and date. Explain identification system.

   Yes. Specimens are coded either by test number date or animal number or code number depending of the specimen.

I. STORAGE AND RETRIEVAL OF RECORDS AND DATA

1. The testing facility maintains and retains all raw data, documentation and other information, protocols, specimens, and final reports generated during and as the result of a nonclinical laboratory study and they are retained in an archive of adequate space and design and are indexed to facilitate their orderly and expedient storage and retrieval.

   Yes.

2. The archive provides the proper conditions to minimize deterioration of all stored material for as long as they are required to be retained.

   Yes.

3. The archive contains specific reference to other locations in which documents and specimens may be stored.

   All materials are kept in the archive.

4. Documents and specimens required to be maintained in the archive and not physically present there have appropriate and specific reference to their location filed in the archive.

   Yes.

5. An individual responsible for the archive is identified.

   Yes.

6. Only authorized personnel enter the archive and whenever a custodian of the archive is not present the suitable repositories for the documents and specimens are locked.

   Yes.

7. Whenever the original material is transferred to the sponsor's archive at the sponsor's request at the completion of the study, duplicates of all material required to be in the archive are retained there, when the nature of the material permits.

   Original material is never transferred to the sponsor's archive.

8. All material required to be retained in the archive is available for inspection to authorized employees of the Food and Drug Administration.

   Yes.

9. If the archive has been contracted out to a commercial archive not belonging to the research facility or sponsor, then the name and address of the commercial archieve has been provided to the sponsor in the submission of the final study report.

   Not applicable.

J. RETENTION OF RECORDS

1. All protocols, raw data, specimens, final reports and other required documents pertinent to the conduct of the study, including records and reports of maintenance, cleaning, calibration and inspection of equipment, are stored in an archive, and retained for the specified time.

   All materials pertinent to the study are kept in the archive. Time depends on the Sponsor request.

2. Curriculum vitae and job descriptions of all personnel engaged in conducting the study are retained for the specified period of time, either in the facility employment records, or the archive; and are available for inspection.

   Data are kept in the administration office.

3. The master schedule sheet, records of inspection or evaluation and status reports of the quality assurance unit are retained for specified period of time.

   No.

K. PERSONNEL

1. Adequate periodic training is provided by well-qualified individuals to assure that each person engaged in a laboratory study continues to be qualified for his/her function.

   Personnel is examined by the Head of Laboratory and by Technical direction.

2. A current curriculum vitae (C.V.) is maintained along with a current job description for each person engaged in the conduct of the study. The testing facility also retains the last available C.V. and job description after termination of employment. (Obtain copies of C.V).

   Yes.

3. The testing facility has a sufficient number of personnel to accomplish the activities specified by the protocol.

   Yes.

4. Persons found to have an apparent illess that may adversely affect the integrity of the study are removed from direct contact with any or all applicable aspects of the study until the condition is corrected. Such facts are documented in the records of the study.

   Yes but these facts are not documented.

L. QUALITY ASSURANCE UNIT

1. Each phase of a study is periodically inspected, written reports are prepared, and corrective actions when required are documented.

   Each phase of a study is not periodically inspected by the Responsible of Ministry of Health.

2. All studies are evaluated for conformity to the protocol as required, deviations from the protocol or standard operating procedures are not made without prior approval, and written records of these activities are maintained. The quality and reliability of work performed by contractors and grantees is monitored.

   Deviations are only written on the final report and on laboratory record.

3. Status reports are submitted to management periodically.

   No.

M. EQUIPMENT

1. Equipment, procedures and materials used to protect the integrity and health of test systems, including pest control, are of appropriate design and type, and do not interfere with the conduct of the study; and,

   Yes.

2. Can be easily cleaned and maintained; and,

   Yes.

3. Is cleaned, inspected and maintained regularly.

   Yes.

4. Equipment and materials used to prepare and administer test and/or control substances are of adequate design to assure accurate administration of these substances; and,

   Yes.

5. To preclude contamination of test and control substances; and,

   Yes.

6. Can be easily cleaned and maintained; and,

   Yes.

7. Is cleaned, inspected, maintained and calibrated regularly.

   Yes.

8. Written records are kept which accurately document all inspection, cleaning, testing, and calibrating operations; and,

   No.

9. Nonroutine maintenance and remedial actions taken because of failure or malfunction.

   Yes.

10. The use of all cleaning, maintenance, and pest control materials which might interfere with the conduct of the study or be hazardous to the test system is adequately documented and does not contaminate test systems.

    Yes.

N. ANIMAL CARE

1. Needs for deviation from the standards for animal care are adequately documented and incorporated in the records of the study.

   Not completely.

2. Environmental factors such as the caging and housing systems, sanitation practices, diet, handling, ventilation, lighting, temperature and noise control are maintained uniformly throughout the course of the studies; and,

   Yes.

3. Changes to new locations, or of anvironmental factors, are not made during the course of the study without written permission from the study director; and the record of the approval and details of the changes are maintained.

   Changes are not made during the course of the study.

4. All newly received animals are kept in quarantine for a predetermined period of time during which their health status is evaluated. (State length of quarantine period for species involved in this study and reasons for disqualifying animals from tje study if applicable).

   Rabbits were kept in quarantine for 20 days in some area of the study.

5. Bedding used in animal cages or pens does not interfere with purpose or conduct of the study.

   Sawdust was used in bottom wire cages.

O. TEST AND CONTROL SUBSTANCES

1. Each batch of a test and control substance is assayed for identity, strength, quality, and purity prior to initiation of the study either by the laboratory or the sponsor who provides verifying documentation with the substances.

   These actions were performed by the Sponsor.

2. Prior to initiation of the study the stability of each test and control substance is determined, where possible, and if not previously determined by the sponsor, unless stability is the purpose of the study.

   Idem as G1.

3. The test and control substances are derived from the smallest number of production batches consistent with their stability and necessary to fulfill the requirements of the study.

   Test substance was derived from one batch.

4. A system for the distribution of the test and control substances is established with procedures to assure that proper storage at all times maintains the identity, strength, quality, purity, and stability of the substances; and,

   Procedures were used "de facto" by verbal indication of the Head of Toxicology.

5. the possibility of cross-contamination of the substance, is precluded; and,

   Yes

6. appropriate identification of the substance is maintained throughout the distribution process; and,

   Yes

7. the receipt and distribution of each batch of the substance is properly documented.

The receipt of batch from the Sponsor is properly documented.

8. If batches of test and control substances are returned from distribution for redistribution, test and control substances are quarantined in a separate and identificable area; the source of the return and the reason for the return are documented.

Every day of administration new flask with lyophilized product was allozed.

9. Batches of the test and control substances to be redistributed are reanalyzed to determine conformance to established specifications and redistributed only if all appropriate standards and specifications are met.

No.

10. Batches of returned test and control substances tha do not conform to appropriate standards and specifications are not distributed without documentation of further appropriate investigations made and corrective actions taken.

No.

P. STUDY IMPLEMENTATION AND CONDUCT

1. A written detailed protocol including statistical methods is available and approved before the study initiation.

   Yes.

2. The protocol contains the name of the sponsor, a descriptive title and statement of purpose; and,

   Initial protocol contains descriptive title and statement of purpose.

3. The name of Study Director, as well as of scientists or professional persons, laboratory assistants and animal care personnel; and,

   only the name of the Study Director.

4. The name and address of any contractors; and,

   name and address of lab. testing.

5. Identification and stability of test and control substances; and,

   Identification of the test substance.

6. Proposed dates for starting completion and submission of final reports; and,

   No.

7. Specifications for thr test systems including source (obtain name and address) and,

   No.

8. Procedure for unique identification of test system if needed, the method for randomization, if any, and its justification: and,

No, but the rabbits were cage individually.

9. Description of the diet used in the study as well as solvents, emulsified and/or other material (s) used to solubilize or suspend the test and control substance before mixing in the carrier.

No.

10. Route of administration of test and control substances and reason for its selection; and,

Yes.

11. Dosage levels (s), method and frequency of administration, and method to measure absorption; and,

Yes, except method to measure absorption.

12. Types and frequency of tests, analyses and measurements, and records to be maintained; and,

Yes.

13. Nonroutine procedures required to assure personnel health and safety.

No.

14. Changes or revisions to an approved protocol are documented, signed by the Study Director, dated and retained with the protocol.

Yes.

15. The Study Director assured that the approved protocol, including revisi
is followed precisely and,

Yes.

16. Test and control substances are appropriately tested; and,

No.

17. Test systems are appropriate for the study; and,

Yes.

18. Personnel recources, facilities, and methodologies are available and,

Yes are described in the final report.

19. Personnel involved in the study understand their responsibilities; and,

Yes in the final report.

20. All data are accurately and promptly verified and recorded including:
The administration of the test and control substances to the appropriat
test systems in the appropriate dosage, by the approproate method and
at the appropriate time, as specified in the protocol (describe in de-
tail; and,

Control of all raw data was made when final report was written.

21. The tracking of a test system life history in order to assure the accu
and consistency of all responses and manifestations observed during th
course of the study. (Describe the tracking system in details and

Partially described in the final report.

29. All data, documentation, other information, protocols, specimens and final reports are transmitted to the archive.

Yes.

30. All data generated during the study are recorded, signed and dated in the required manner.

Not always. It was not ufficially requested at this period.

31. Test systems are monitored in conformity with the protocol.

Yes.

32. Animals moribund or found dead during a study are necropsied as specified in the protocol. Explain the operational procedures.

Yes. Procedures of the action are documented in the record and final report.

22. The age at sacrifice/death for each test and control test system; and,

Yes.

23. Gross pathology findings which are available to the pathologist examining the specimen microscopically, and

Yes.

24. Unforseen circumstances that may affect the quality and integrity of the study are noted and documented; and,

Yes.

25. Unexpected health hazards to test systems are promptly reported to the appropriate supervisor and that corrective action taken is documented; and,

Yes corrective actions were taken if available and documented in the record.

26. The responses of test systems are documented; and,

Yes.

27. All required GLPs are followed; and

At the time when the study was conducted GLP were not available.

28. The study is carried out in a manner that provides for safety for laboratory personnel, and,

Yes.

O. REQUIRED DESCRIPTIVE OR QUANTITATIVE INFORMATION FOR COMPLETED ANIMAL STUDIES ONLY

a. Species being used in the study

New Zealand rabbits.

b. Length of time that the animals were on study

20 days for quarantine

30 days for the study

c. Number of animals loaded into the study:

1. on test substance : 24
2. on control : 12

d. Number of animals:

1. on test substance found dead : none
2. on test substance sacrificed : 24
3. on control found dead : none
4. on control sacrificed : 12

P. REPORTING OF NONCLINICAL LABORATORY STUDY RESULTS

1. The final report shall contain the name and address of the facility performing the study, and

Yes.

2. dates on which study was initiated and completed; and,

Yes.

3. the identity of the test and control substances, and

Yes.

4. the name of the Study Director, and

Yes.

5. A summary of data, and analysis of data, and a statement of the conclusions drawn from the analysis, and

Yes.

6. reports of each individual scientist or other professional persons involved in the study, appropriately signed and dated and,

No.

7. the location where all raw data and the final report are to be stor

Yes, but not precisely the room and the rack.

8. The final report describes the objectives and procedures stated in the approved protocol, and

Yes.

9. the data elements collected during the study, and

Yes.

10. the statistical methods employed for analysing the data, and

Yes.

11. the stability of the test and control substances under the conditions of administration, and

No, see the report, the test substance was lyophilized and solution was prepared at the moment of the administration.

12. the methods used, and

Yes.

13. the test system used, and

Yes.

14. the dosage, dosage regimen, route of administration and duration; and,

Yes.

15. any unforeseen circumstance that may have affected the quality or integrity of thr nonclinical laboratory study.

Yes, if it is available.

16. Amendments to the final report are clearly identified, justified, siged and dated.

No, the final report relates the correct execution of the study.

Cent... ...ceutica S.p.A.

CRF

TERATOLOGY - EXP Nº 023 - STRAIN "NEW ZEELAND "

STATISTICAL ANALYSIS OF RESULTS

	I GROUP	II GROUP	CONTROL	F e X^2 for comparisons					
				I	→ ←	II	→ ←	F	TOT.
Nº implants	10,7 ± 0,78	9,5 ± 0,40	8,8 ± 0,80	2,9	N.S.	0,6	N.S.	2,0	N.S.
Nº fetuses	10,3 ± 0,86	9,4 ± 0,37	8,5 ± 0,99	1,9	N.S.	0,7	N.S.	1,3	N.S.
Nº alive born	10,0 ± 0,78	8,8 ± 0,47	8,2 ± 0,89	2,4	N.S.	0,4	N.S.	1,6	N.S.
Nºstillborn (/total)	0/110	0/88	0/90	X^2 -	-	-	-	-	-
(/mothers)	0/11	0/10	0/11	X^2 -	-	-	-	-	-
Reabsorption (/total)	5/118	1/95	4/97	X^2 0,09	N.S.	0,78	N.S.	-	-
(/mothers)	3/11	1/10	1/11	X^2 0,34	N.S.	0,45	N.S.	-	-
Abortions(/total)	3/113	6/94	3/93	X^2 0,03	N.S.	0,44	N.S.	-	-
(/mothers)	3/11	3/10	3/11	X^2 0,02	N.S.	0,11	N.S.	-	-
Corpus luteum: right	6,1 ± 0,44	4,6 ± 0,34	4,9 ± 0,44	3,7	N.S.	0,3	N.S.	3,7	< 0,05
left	5,0 ± 0,56	5,0 ± 0,39	4,0 ± 0,50	1,8	N.S.	2,4	N.S.	1,4	N.S.
ex: male	4,7 ± 0,56	4,3 ± 0,40	3,5 ± 0,43	3,2	N.S.	2,0	N.S.	1,9	N.S.
female	5,3 ± 0,56	4,5 ± 0,52	4,7 ± 0,62	0,4	N.S.	0,1	N.S.	0,5	N.S.
etus weight: male	32,49 ± 0,843	34,79 ± 0,871	35,54 ± 1,214	4,6	< 0,05	0,3	N.S.	2,9	N.S.
female	31,05 ± 1,108	35,04 ± 0,852	33,33 ± 0,974	2,4	N.S.	1,7	N.S.	3,9	< 0,025
TOTAL	31,72 ± 0,702	34,92 ± 0,605	34,26 ± 0,765	5,9	< 0,025	1,5	N.S.	6,1	< 0,005

DATA: 20/9/77

FIRMA: [illegible]

TERATOLOGY - EXP. N° 023 - STRAIN "NEW ZEELAND"

VISCERAL AND SKELETAL ANOMALIES IN "NEW ZEELAND" FEMALE RABBIT TREATED WITH ESAFOSFINA

	DOSES		
	I GROUP 200 mg/Kg i.v.	II GROUP 100 mg/Kg i.v.	III GROUP 0 (Control)
Observations:			
VISCERAL			
N° examined (fetuses/mothers)	110/11	88/10	90/11
		no abnormalities	
SKELETAL			
N° examined (fetuses/mothers)	65/11	51/10	55/11

	Fetuses	Mothers	Fetuses	Mothers	Fetuses	Mothers
Fetuses with reduced somatic size	4	2	0	0	2	1
Supernumerary ribs	30	11	20	9	13	7
Lack of the 6th point of ossification	8	5	10	5	12	7
Open bregma	3	2	1	1	2	1

DATA: 20/9/77

FIRMA: C.R.F. Consiglio Ricerche Farmacologiche Dr. Alfredo Sanfilippo

GROUP 1 STRAIN 'NEW ZEELAND' EXPERIMENT CRF 023 TREATMENT : FDP 200 mg/Kg i.v. SUMM. TERAT. CARD

		Born				Corpus luteus		Sex		fetus weights		
s	N° Implants	Fetuses	Alive	dead	Reabsorption	Abortion	right	left	M	F	M	F	TOTAL
	10,7	10,3	10,0	-	-	-	6,1	5,0	4,7	5,3	32,49	31,05	31,72
	0,78	0,86	0,78	-	-	-	0,44	0,56	0,56	0,56	0,843	1,108	0,702
	9,0-12,5	3,3-12,2	8,3-11,8	-	-	-	5,1-7,1	3,8-6,2	3,5-6,0	4,0-6,5	30,80-34,18	28,83-33,27	30,33-33,11
compared to fetuses				0/110	5/118	3/113	-	-	-	-	-	-	-
compared to mothers				0/11	3/11	3/11	-	-	-	-	-	-	-

DATA: 21/9/77 FIRMA: C. R. A. CONSORZIO RICERCA ... S.p.A. Dr. Alfredo Manzitta

GROUP I STRAIN " **NEW ZEELAND** " EXPERIMENT **CRF 023** TREATMENT : **FDP 200 mg/Kg** i.v. SUMM.TERAT.CARD

Rabbit N°	N° Implants	BORN Fetuses	Alive	dead	Reabsorptions	Abortion	CORPUS LUTEUS right	left	SEX M	F	WEIGHT OF FETUSES M	F
1	8	8	8	-	-	-	4	4	4	4	37,7-30,2-31,0 30,7	31,8-20,5-39, 21,4
2	N.G.	-	-	-	-	-	-	-	-	-	-	-
3	11	11	11	-	-	-	7	4	6	5	35,3-26,9-29,5 31,0-33,6-30,5	37,1-30,7-33, 33,7-29,0
4	7	7	7	-	-	-	8	1	3	4	38,9-38,0-39,0	33,2-44,7-42,
5	8	5	5	-	3	-	5	5	2	3	42,9-41,4	47,4-40,6-47,
6	14	13	12	-	1	1	6	8	4	8	36,2-33,4-38,0 26,5	28,7-25,9-32, 32,3-29,2-44, 44,2,32,1
7	12	11	11	-	1	-	7	5	6	5	34,0-31,4-28,3 29,7-30,2-41,8	30,1-33,6-32, 30,0-27,9
8	11	11	11	-	-	-	5	6	7	4	32,8-35,2-28,4 30,6-30,8-31,8 34,5	29,9-35,6-30, 32,6
9	14	14	13	-	-	1	8	6	5	8	20,5-24,2-21,4 18,4-18,5	23,4-20,5-16, 10,0-24,3-20, 16,6-11,9
10	12	12	12	-	-	-	7	5	4	8	37,5-36,6-33,0 21,2	37,5-32,3-30, 24,0-16,3-28, 27,7-31,5
11	13	13	12	-	-	1	6	7	8	4	37,2-32,2-41,1 37,8-30,3-33,5 36,0-23,8	30,7-35,2-36, 37,6
12	8	8	8	-	-	-	4	4	3	5	42,5-37,0-36,5	30,2-41,6-34, 21,0-43,4

C. R. F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.

GROUP II STRAIN 'NEW ZEELAND' EXPERIMENT CRF 023 TREATMENT : FDP 100 mg/Kg i.v. SUMM. TREAT. CARD

Rabbits	N° Implants	BORN Fetuses	Alive	Dead	Reabsorptions	Abortion	CORPUS LUTEUS right	left	SEX M	F	FETUS WEIGHTS M	F	T
1	N.G.	-	-	-	-	-	-	-	-	-	-	-	
2	7	7	7	-	-	-	3	4	5	2	37,1-33,6-35,2 32,3-35,4	32,9-38,6	
3	9	9	8	-	-	1	5	3	3	5	33,5-35,3-35,8	40,7-36,0-36,8 37,2-42,4	
4	11	10	10	-	1	-	4	7	4	6	40,7-37,0-34,2 28,6	30,7-29,0-21,8 36,1-31,8-45,0	
5	10	10	10	-	-	-	5	6	7	3	31,9-34,7-32,6 38,8-33,3-33,0 35,7	33,4-34,5-34,3	
6	10	10	10	-	-	-	6	4	5	5	32,5-25,3-31,5 31,4-23,6	35,0-35,6-36,3 29,1-44,4	
7	8	8	8	-	-	-	3	5	5	3	43,0-42,3-36,0 37,6-46,4	35,2-36,0-37,7	
8	10	10	6	-	-	4	4	6	3	3	52,0-29,5-26,3	34,7-31,0-28,6	
9	N.G.	-	-	-	-	-	-	-	-	-	-	-	
10	10	10	10	-	-	-	5	5	4	6	37,4-32,4-42,1 39,9	37,7-39,2-35,7 36,9-37,3-39,3	
11	11	11	10	-	-	1	6	6	3	7	29,2-21,8-33,4	34,9-27,9-31,0 32,4-32,6-30,9 25,2	
12	9	9	9	-	-	-	5	4	4	5	31,0-38,3-37,4 37,1	30,9-34,5-27,1 48,0-38,3	

C. R. F.
Dr. Alfredo Nunziata

GROUP II STRAIN 'NEW ZEELAND' EXPERIMENT CRF 023 TREATMENT : FDP 100 mg/Kg i.v. SUMM. TERAT. CARD

Rabbits N.	N° Implants	BORN Fetuses	Alive	Dead	Reabsorptions	Abortions	CORPUS LUTEUS right	left	SEX M	F	FETUS WEIGHTS M	F	
M	9,5	9,4	8,8	-	-	-	4,6	5,0	4,3	4,5	34,79	35,04	34,92
± ES	0,40	0,37	0,47	-	-	-	0,34	0,39	0,40	0,52	0,871	0,852	0,605
L.F.	8,6-10,4	8,6-10,2	7,7-9,9	-	-	-	3,8-5,4	4,1-5,9	3,4-5,2	3,3-5,7	33,03-36,55	33,32-36,76	33,72-36,12
n/t compared to fetuses				0/88	1/95	6/94	-	-	-	-	-	-	-
n/t compared to mothers				0/10	1/10	3/10	-	-	-	-	-	-	-

DATA: 21/9/77

FIRMA: C.R.F. ASSOCIAZIONE RICERCA FARMACEUTICA S.p.A. Dr. Alfredo Fumagalli

CRF

GROUP III STRAIN NEW ZEELAND EXPERIMENT CRF 023 TREATMENT: Physiol. Solution SUMM. TERAT. CARD

Rabbit	N° Implants	BORN Fetuses	BORN Alive	BORN dead	Reabsorptions	Abortion	CORPUS LUTEUS right	CORPUS LUTEUS left	SEX M	SEX F	FETUS WEIG M	
1	N.G.	-	-	-	-	-	-	-	-	-	-	
2	6	2	2	-	4	-	3	5	1	1	44,5	42,5
3	9	9	9	-	-	-	5	4	4	5	29,0-40,6-33,9 31,7	24,0-32 25,5-28
4	7	7	7	-	-	-	4		3	4	35,6-25,2-35,7	32,0-31 36,1
5	10	0	10	-	-	-	6	4	5	5	43,7-41,0-29, 31,4-29,6	26-29 30,3-28
6	13	13	12	-	-	1	7	6	5	7	21,2-26,3-28,2 26,1-26,2	27,8-25 26,9-35 26,7
7	9	9	9	-	-	-	5	4	4	5	33,5-37,5-26,9 29,9	23,8-31 30,1-22
8	4	4	4	-	-	-	3	1	1	3	41,3	44,7-42
9	12	12	11	-	-	1	4	7	3	8	37,0-39,9-26,9	28,7-28 41,0-30 38,2-25
10	8	8	8	-	-	-	6	2	5	3	42,6-43,4-35,3 44,4-36,5	29,7-40
11	11	11	11	-	-	1	7	4	3	7	35,4-47,1-49,4	29 26-28 34,6
12	8	8	8	-							45,4-52,6-49,7 36,5	

J.M.R.

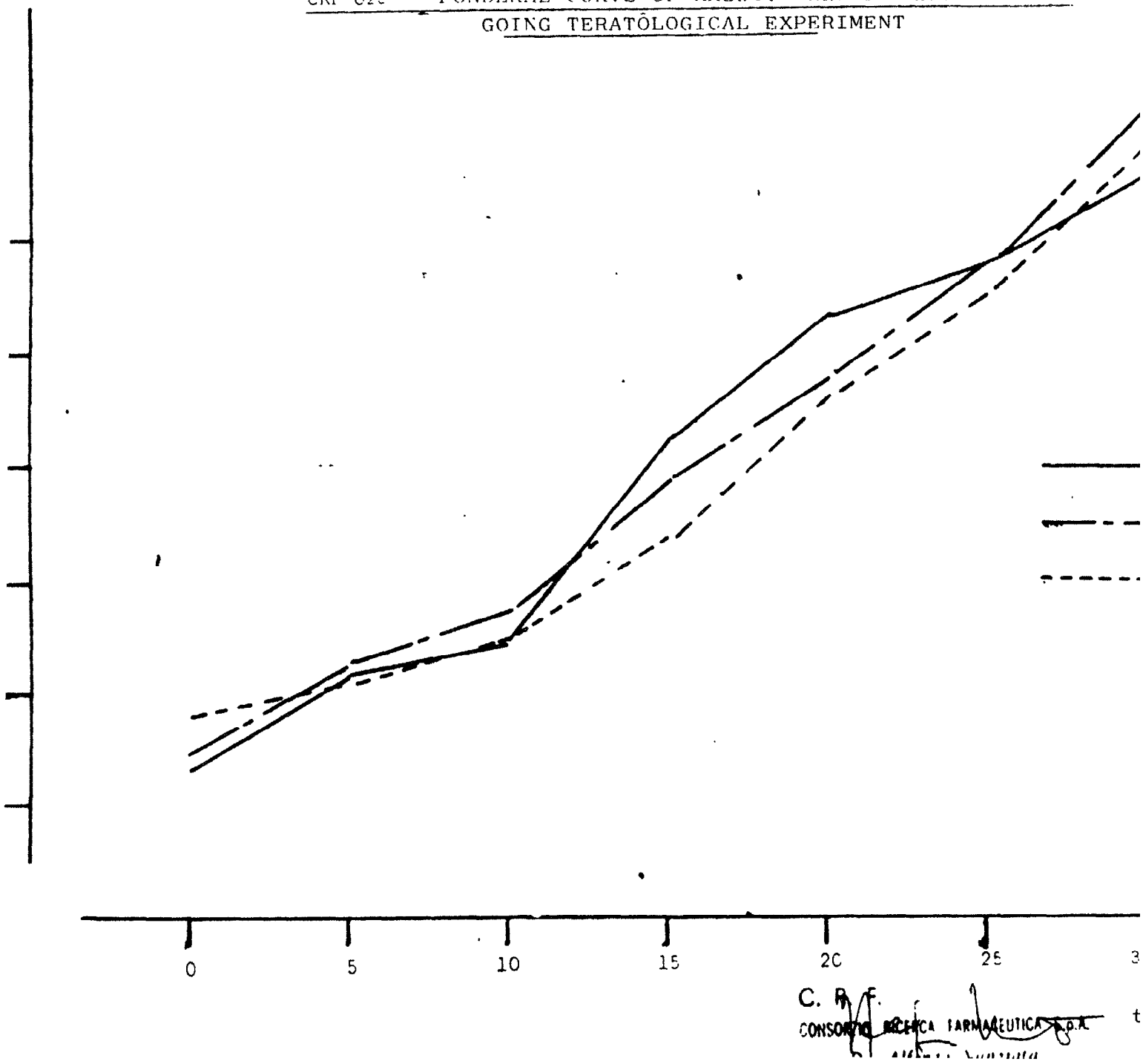
GROUP III STRAIN 'NEW ZEELAND' EXPERIMENT CRF 023 TREATMENT : Physiol. solution SUMM. TERAT. CARD

	N°	BORN			Reabsor		CORPUS LUTEUS		SEX .		FETUS WEIGHTS		
	N°Implants	Fetuses	Alive	Dead	ptions	Abortion	right	left	M	F	M	F	TOTAl
	8 ,8	8,5	8,2	-	-	-	4,9	4,0	3,5	4,7	35,54	33,33	34,26
;	0, 80	0,99	0,89	-	-	-	0,44	0,50	0,43	0,62	1,214	0,974	0,765
	7,1- 10,6	6,3-10,7	6,2-10,2	-	-	-	4,0-5,9	2,9-5,1	2,5-4,4	3,4-6,1	33,08-38,00	31,37-35,28	33,50-35,0
	mpared to fetuses			0/90	4/97	3/93	-	-	-	-	-	-	-
	mpared to mothers			0/11	1/11	3/11	-	-	-	-	-	-	-

DATA: 21/9/77

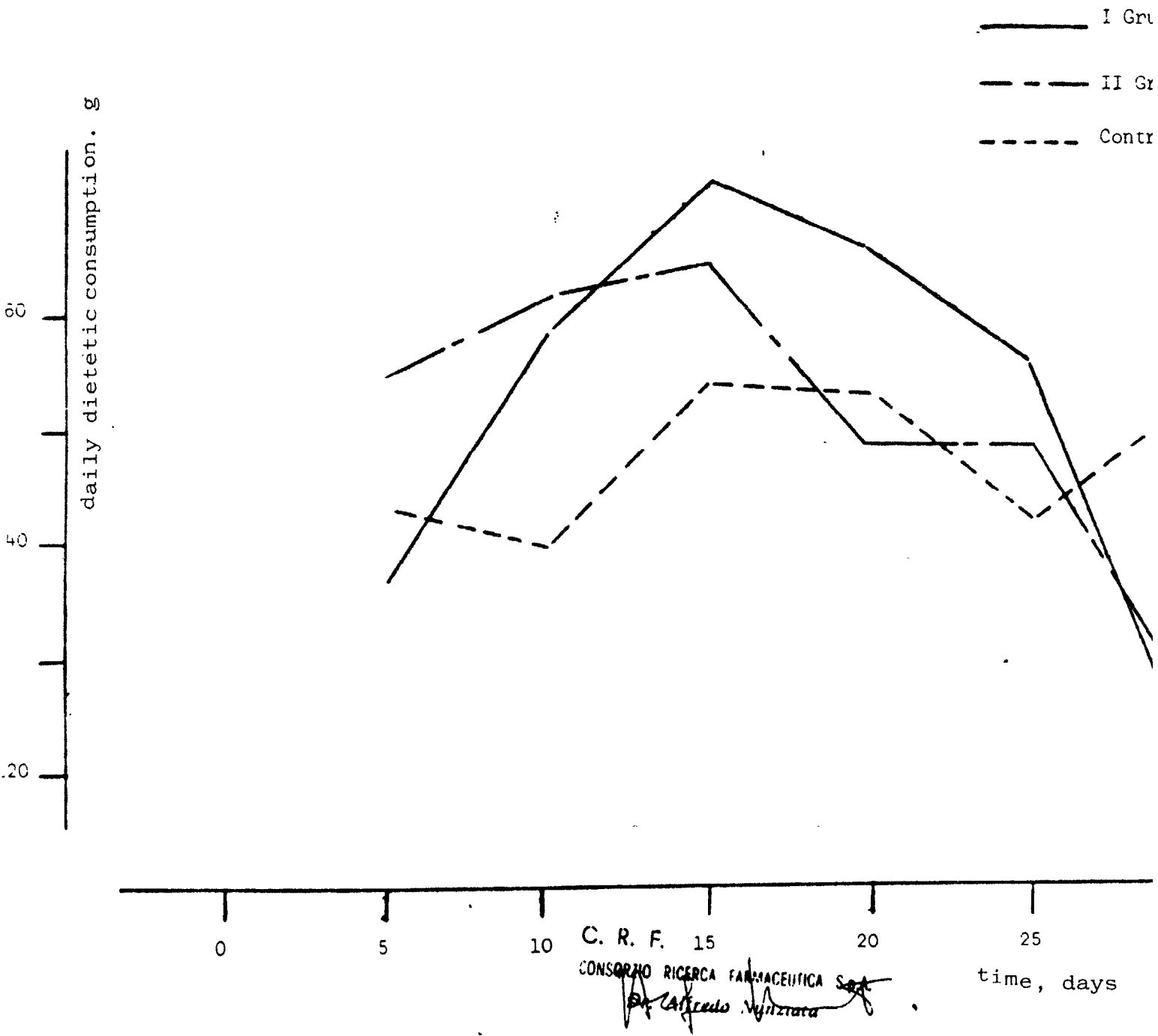
FIRMA: C.R.F. CONSORZIO PER LA RICERCA SPERIMENTALE SRL
Dr. Alfredo Nanziata

CRF 023 - PONDERAL CURVE OF RABBIT "NEW ZEELAND" UNDERGOING TERATOLOGICAL EXPERIMENT



C. R. F.
CONSORZIO RICERCA FARMACEUTICA S.p.A.

CRF 023 - MEAN DIETETIC CONSUMPTION OF "NEW ZEELAND"RABBIT DURING PREGNANCY PERIOD



C. R. F.

CONSORZIO RICERCA FARMACEUTICA S.r.l.

CRF consorzio ricerca farmaceutica

Teratologi N° 023

rabbit N° 1 group I° treatment Esafosfina 200 mg/K .e

beginning of pregn. 4/1/77 beginning of treat. 10/1/77

end of treatment 22/1/77 delivery 2/2/77

A	n° implants (A = G+H+F+E)	8
B	n° fetuses (B = G+H+F)	8
C	n° alive	8
D	n° dead	-
E	n° reabsorption	-
F	n° abortions	-
G	n° male born	4
H	n° female "	4
I	n° corpus luteus-right	4
L	n° corpus luteus-left	4

time	Animal weight g	dietetic consumption
0	3280	
5	3340	140
10	3420	150
15	3540	160

weight fetuses, g	sex
31,8	F
20,5	F
39,9	F
21,4	F
37,7	M
30,2	M
31,0	M
30,7	M

Observations

Supernumerary ribs in 3 cas

Fetuses with reduced somati size in 3 cases

CRF consorzio ricerca farmaceutica

Teratology n° 023 ....

rabbit 2 group I° treatment Esafosfina 200 mg/K. e

beginning of pregnancy 4/1/77 beginning of treat 10/1/77.

end of treatment 22/1/77 delivery 3/2/77

No pregnant

A n° implants
(A = G+H+F+E)

B n° fetuses
(B = G+H+F)

C n° alive

D n° dead

E n° reabsorption

F n° abortions

G n° male born

H n° female "

I n° corpus luteus - right

L n° corpus luteus - left

Observations

time	Animal weight g	dietetic consumtion
0	3500	
5	3590	180
10	3430	190
15	3420	190
20	3480	156

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Dr. Alfredo Nunziata

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Teratology 023

rabbit 3 group I° treatment ESAFOSFINA 200 mg/K

beginning of pregnancy 4/1/77 beg. of treatment 10/1/77

end of treatment 22/1/77 delivery 2/2/77

A	n°Implants (A = G+H+F+E)	11	fetus weight,g	sex
B	n°Fetuses (B = G+H+F)	11	35,3	M
			26,9	M
C	n°Alive	11	29,3	M
D	n°Dead	-	31,0	M
E	n°Reabsorptions	-	33,6	M
F	n°Abortions	-	30,5	M
G	n°male born	6	37,1	F
			30,7	F
H	n°female born	5	33,5	F
I	n°Corpus luteus-right	7	33,7	F
L	n°Corpus luteus-left	4	29,0	F

Observations

time	animal weight g	dietetic consumption
0	3480	
5	3520	180
10	3500	196
15	3460	200
20	3660	192
25	3800	180

supernumerary ribs in 2 cases

C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nunziata

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Teratology .023. ..... Esafosfi

rabbit ...4..... group ...I°..... treatment 200 mg/l

beginning of pregn..18/1/77.....beginning of treat.24/1/77.

end of treatment ..5/2/77.....delivery ...17/2/77.....

A	n° Implants (A = G+H+F+E)	7
B	n° Fetuses (B = G+H+F)	7
C	n° Alive	7
D	n° dead	-
E	n° Reabsorptions	-
F	n° Abortions	-
G	n° male born	3
H	n° female born	4
I	n° corpus luteus-right	1
L	n° corpus luteus-left	8

Fetus weight,g	sex
38,9	M
38,0	M
39,0	M
33,2	F
44,7	F
42,3	F
35,2 --	F

Observations

Supernumerary rib in 4 case

time	animal weight	dietetic consumption
0	2960	
5	3050	140
10	3180	160
15	3250	150
20	3500	184

R. 5

CRF consorzio ricerca farmaceutica

Teratology ..023. .....

Esafosfina

rabbit n° ..5..... group ..I°..... treatment 200 mg/k ev .....

beginning of pregn. ..18/1/77.....beginning of treat....24/1/77.....

end of treatment ..5/2/77.....delivery .....17/2/77.....

A	n° Implants (A = G+H+F+E)	8
B	n° fetuses (B = G+H+F)	5
C	n° alive	5
D	n° dead	-
E	n° reabsorption	3
F	n° abortions	-
G	n° male born	2
H	n° female born	3
I	n° corpus luteus-right	5
L	n° corpus luteus-left	5

fetus weight,g	sex
42,9	M
41,4	M
47,4	F
40,6	F
47,6	F

Observations

- supernumerary ribs in 1 case

time	animal weight,g	dietetic consumption
0	2800	
5	2860	120
10	2800	80
15	2930	140
20	3020	152
25	3150	148
30	3260	160

C.R.F. CONSORZIO RICERCA FARMACEUTICA S.p.A.
Dr. Alfredo Nuti

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Teratology 023

Esafosfina

rabbit n° 6 group I° treatment 200 mg/K ev

beginning of pregn. 18/1/77 beginning treat. 24/1/77

end of treatment 5/2/77 delivery 17/2/77

A	n° Implants (A = G+H+F+E)	14
B	n° Fetuses (B = G+H+F)	13
C	n° alive	12
D	n° dead	-
E	n° reabsorptions	1
F	n° abortions	1
G	n° male born	4
H	n° female born	8
I	n° corpus luteus-right	6
L	n° corpus luteus-left	8

fetus weight,g	sex
36,2	M
33,4	M
38,0	M
26,5	M
28,7	F
25,9	F
32,3	F
32,3	F
29,2	F
44,8	F
42,2	F
37,1	F

Observations

supernumerary ribs in 4 cases

open bregma in 1 case

0	3350	
5	3410	130
10	3420	124
15	3550	162
20	3780	170
25	4000	170
30	4060	180

C. R. F. Consorzio Ricerca Farmacologica S.p.A. Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica

Teratology ...023....

rabbit n° ..7.....group ....I°.....treatment Esafosfina 200 mg/K ev

beginning of pregn. ..1/2/77.....beginning treat....7/2/77.....

end of treatment ...19/2/77.....delivery ....2/3/77.....

A	n° implants (A = G+H+F+E)	12
B	n°fetuses (B = G+H+F)	11
C	n°alive	11
D	n°dead	–
E	n° reabsorptions	1
F	n°abortions	–
G	n°male born	6
H	n°female born	5
I	n°corpus luteus-right	7
L	n°corpus luteus-left	5

fetus weight,g	sex
34,0	M
31,4	M
28,3	M
29,7	M
30,2	M
41,8	M
30,1	F
33,6	F
32,9	F
30,0	F
27,9	F

time	animal weight g	dietetic consumption
0	3180	
5	3220	180
10	3380	180
15	3520	150
20	3620	190
25	3450	140

Observations

Supernumerary ribs in 2 cases

lack of 6th point of ossificatio in 1 case

C.R.F. Consorzio Ricerca Farmaceutica S.p.A.
Dr. Alfredo N...

CRF Consorzio ricerca farmaceutica

Teratology 023

rabbit n° 8 group I° Esafosfine treatment 200 mg/k i.v.

beginning of pregn. 1/2/77 beginning of treat. 7/2/77

end of treatment 19/2/77 delivery 2/3/77

A	n° Implants (A = G+H+F+C)	11	
B	n° fetuses (B = G+H+F)	11	
C	n° alive	11	
D	n° dead	-	
E	n° reabsorptions	-	
F	n° abortions		
G	n° male born		
H	n° female born	4	
I	n° Corpus luteus-right	5	
L	n° corpus luteus-left	6	

32,5	
35,2	
29,4	
30,6	
30,8	
31,4	
34,5	
29,9	
35,6	
30,8	
32,6	

Observations

supernumerary ribs in 2 cases

open bregma in 2 cases

time	animal weight	dietetic consumption
	2770	
	2740	160
	2660	148
	2700	140
	2[illegible]2	124
		136

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Teratology 023

rabbit n° 9 group I° treatment Esafosfina 200 mg/K ev

beginning of pregn. 1/2/77 beginning of treat. 7/2/77

end of treatment 19/2/77 delivery 2/3/77

A	n° Implants (A = G+H+F+E)	14
B	n° fetuses (B = G+H+F)	14
C	n° alive	13
D	n° dead	-
E	n° reabsorptions	-
F	n° abortions	1
G	n° male born	5
H	n° female born	8
I	n° corpus luteus-right	8
L	n° corpus luteus-right	6

fetus weight, g	sex
20,5	M
24,2	M
21,4	M
18,4	M
18,5	M
23,4	F
20,5	F
16,4	F
24,3	F
20,2	F
16,6	F
10,0	F
17,9	F

Observations: highly hypotrophi

supernumerary ribs in 1 case

lack of 6th point of ossificatio

in 1 case

time	animal weight g	dietetic consumption
0	3030	
5	2980	120
10	3080	160
15	3120	164
20	3200	150
25	3030	100

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Teratology 023

rabbit n° 10 group I° treatment Esafosfina 200 mg/k ev

beginning pregn. 22/2/77 beginning treat 28/2/77

end of treatment 12/3/77 delivery 23/3/77

A	n° implants (A = G+H+F+E)	12
B	n° fetuses (B = G+H+F)	12
C	n° alive	12
D	n° dead	-
E	n° reabsorptions	-
F	n° abortions	-
G	n° male born	4
H	n° female born	8
I	n° corpus luteus-right	7
L	n° corpus luteus-left	5

fetus weight, g	sex
37,5	M
36,6	M
33,0	M
21,2	M
37,5	F
32,3	F
30,0	F
24,0	F
16,3	F
28,3	F
27,7	F
31,5	F

time	animal weight	dietetic consumption
0	2920	
5	2900	128
10	2950	100
15	3100	136
20	3150	110
25	3220	80

Observations

supernumerary ribs in 4 cases

lack of 6th point of ossification in 1 case

G R F

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Teratology n° ..023.....

rabbit n° 11..... group I°..... treatment Esafosfina 200 mg/K ev.....

beginning of pregn. 22/2/77.....beginning of treat 28/2/77.....

end of treatment 12/3/77..... delivery 23/3/77.....

A	n°Impalnts (A = G+H+F+E)	13
B	n°fetuses (B = G+H+F)	13
	n°alive	12
D	n°dead	–
E	n°reabsorptions	–
F	n°abortions	1
G	n°male born	8
H	n°female born	4
I	n°corpus luteus right	7
L	n°corpus luteus left	6

fetus weight,g	sex
37,2	M
32,2	M
41,1	M
37,8	M
30,3	M
33,5	M
36,0	M
23,8	M
30,7	F
35,2	F
36,5	F
37,6	F

Observations

supernumerary ribs in 3 cases

lack of 6th point of ossificatio in 3 cases

time	animal weight	dietetic consumption
0	3180	
5	3200	150
10	3250	144
15	3380	140
20	3500	166
25	3660	160
30	3900	160

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Teratology n° 023

rabbit n° 12 group I° treatment Esafosfina 200 mg/K ev

beginning of pregn. 22/2/77 beginning of treat 28/2/77

end of treatment 12/3/77 delivery 23/3/77

A	n°	Implants (A = G+H+F+E)	8
B	n°	fetuses (B = G+H+F)	8
C	n°	alive	8
D	n°	dead	-
E	n°	reabsorptions	-
F	n°	abortions	-
G	n°	male born	3
H	n°	female born	5
I	n°	corpus luteus-right	4
L	n°	corpus luteus-left	4

fetus	weight, g	sex
	42,5	M
	37,0	M
	36,5	M
	30,2	F
	41,6	F
	34,4	F
	21,0	F
	43,3	F

time	animal weight	dietetic consumption
0	2940	
5	3050	126
10	3000	100
15	3050	140
20	3050	80
25	3330	105
30	3380	110

Observations

supernumerary ribs in 4 case

lack of 6th point of ossification in 2 cases

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Teratology ...023.....

rabbit ...1.....group ...II°.....treatment Esafosfina 100 mg/K ev.....

beginning of pregn. .4/1/77..... treatment .10/1/77.....

end of treatment .22/1/77..... delivery ...2/2/77.....

A n° Implants
(A = G+H+F+E)

B n° fetuses
(B = G+H+F)

C n° alive

D n° dead

E n° reabsorptions

F n° abortions

G n° male born

H n° female born

I n° corpus luteus-right

L n° corpus luteus-left

fetus weight,g sex

Not pregnant

Observations

time	animal weight	dietetic consumption
0	2750	
5	2880	130
10	3000	110
15	3050	100
20	3200	144
25	3200	156
30	3160	240

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Teratology .023.. .....

rabbit n° ..2..... group ..II°..... treatment Esafosfina 100 mg/K ev .....

beginning of pregn. ...4/1/77.....beginning of treat. 10/1/77.....

end of treatment ..22/1/77..... delivery 2/2/77.....

A	n° Implants (A = G+H+F+E)	7
B	n° fetuses (B = G+H+F)	7
C	n° alive	7
D	n° dead	-
E	n° reabsorptions	-
F	n° abortions	-
G	n° male born	5
H	n° female born	2
I	n° corpus luteus-right	3
L	n° corpus luteus-left	4

fetus weight, g	sex
32,9	F
38,6	F
37,1	M
33,6	M
35,2	M
32,3	M
35,4	M

Observations

supernumerary ribs in 3 cases

time	animal weight	dietetic consumtion
0	3280	
5	3320	145
10	3350	140
15	3380	160
20	3400	110
25	3470	110
30	3530	110

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Teratology n° 023

rabbit n° 3 group II° treatment Esafosfina 100 mg/K ev

beginning of pregn. 4/1/77 beginning of treat 10/1/77

end of treatment 22/1/77 delivery 2/2/77

A	n° Implants (A = G+H+F+E)	9
B	n° fetuses (B = G+H+F)	9
C	n° alive	8
D	n° dead	–
E	n° reabsorptions	–
F	n° abortions	1
G	n° male born	3
H	n° female born	5
I	n° corpus luteus-right	5
L	n° corpus luteus-left	3

fetus weights, g	sex
40,7	F
36,0	F
36,8	F
37,2	F
42,4	F
33,5	M
35,3	M
35,8	M

time	animal weight	dietetic consumption
0	3450	
5	3520	165
10	3550	176
15	3770	180
20	3800	142
25	3800	130

Observations

supernumerary ribs in 2 cases

lack of 6th point of ossification in 2 cases

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Teratology n° 023

rabbit n° 4 group IIo treatment Esafosfina 100 mg/K ev

beginning of pregn. 4/1/77 beginning of treat. 10/1/77

end of treatment 22/1/77 delivery 2/2/77

A	n° Implants (A = G+H+F+E)	11
B	n° Fetuses (B = G+H+F)	10
C	n° alive	10
D	n° dead	-
E	n° reabsorptions	1
F	n° abortions	-
G	n° male born	4
H	n° female born	6
I	n° corpus luteus-right	4
L	n° corpus luteus-left	7

Fetus weight,g	sex
40,7	M
37,0	M
34,2	M
28,6	M
30,7	F
29,0	F
21,8	F
26,1	F
31,8	F
45,0	F

Observations

supernumerary ribs in 1 case

time	animal weight,g	dietetic consumption
0	3630	
5	3720	190
10	3720	200
15	3860	200
20	3960	200
25	4050	200
	122	

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Teratology n°. 023

Esafosfina

rabbit n° 5 group II° treatment 100 mg/K ev

beginning of pregn. 4/1/77 beginning of treat. 10/1/77

end of treatment 22/1/77 delivery 2/2/77

A	n° Implants (A = G+H+F+E)	10
B	n° Fetuses (B = G+H+F)	10
C	n° alive	10
D	n° dead	–
E	n° reabsorptions	–
F	n° abortions	–
G	n° male born	7
H	n° female born	3
I	n° corpus luteus-right	5
L	n° corpus luteus-left	5

fetus weight,g	sex
33,4	F
34,5	F
34,3	F
31,9	M
34,7	M
32,6	M
38,8	M
33,3	M
33,0	M
35,7	M

time	animal weight	dietetic consumption
0	3200	
5	3270	175
10	3330	188
15	3450	200
20	3560	194
25	3700	162
30	3750	135

Observations

supernumerary ribs in 2 cases

lack of the 6th point of ossification in 4 cases.

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teratology n° 023

Esafosfina

rabbit n° 6 group II° treatment 100 mg/K ev

beginning of pregn. 18/1/77 beginning of treat. 24/1/77

end of treatment 5/2/77 delivery 17/2/77

A	n° Implants (A = G+H+F+E)	10
B	n° fetuses (B = G+H+F)	10
C	n° alive	10
D	n° dead	-
E	n° reabsorptions	-
F	n° abortions	-
G	n° male born	5
H	n° female born	5
I	n° corpus luteus-righ	6
L	n° corpus luteus-left	4

fetus weight,g	sex
32,5	M
25,3	M
31,5	M
31,4	M
23,6	M
35,0	F
35,6	F
36,3	F
29,1	F
44,4	F

time	animal weight,g	dietetic consumtion
0	2520	
5	2570	125
10	2600	136
15	2650	100
20	2700	100
25	2730	90
30	2950	110

Observations

supernumerary ribs in 5 cases

lack of 6th point of ossification in 1 case

open bregma in 1 case

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Teratology n°023

rabbit n° 7 group II° treatment Esafosfina 100 mg/K ev.

beginning of pregn. 18/1/77 beginning of treat. 24/1/77

end of treatment 5/2/77 delivery 17/2/77

A	n° Implants (A = G+H+F+E)	8
B	n° fetuses (B = G+H+F)	8
C	n° alive	8
D	n° dead	-
E	n° reabsorptions	-
F	n° abortions	-
G	n° male born	5
H	n° female born	3
I	n° corpus luteus-right	3
L	n° corpus luteus-left	5

fetus weights,g	sex
43,0	M
42,3	M
36,0	M
37,6	M
46,4	M
35,2	F
36,0	F
37,7	F

time	animal weight,g	dietetic consumtion
0	2840	
5	2920	150
10	3000	144
15	3150	170
20	3410	152
25	3480	138

Observations

supernumerary ribs in 3 cases

lack of tHe 6th point of ossification in 2 cases.

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Teratology n° 023

rabbit n° 9 group IIº treatment Esafosfina 100 mg/K ev

beginning of pregnan. 1/2/77 beginning of treat. 7/2/77

end of treatment 19/2/77 delivery 2/3/77

A nº Implants
(A = G+H+F+E)

B nº fetuses
(B = G+H+F)

C nº alive

D nº dead

E nº reabsorptions

F nº abortions

G nº male born

H nº female born

I nº corpus luteus- right

L nº corpus luteus-left

Fetus weights,g sex

Not pregnant

Observations

time	animal weight,g	dietetic consumption
0	2780	
5	2890	136
10	2880	144
15	3120	144
20	3120	146
25	3200	140
		100

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Teratology n° 023

rabbit n° 10 group II° treatment Esafosfina 100 mg/K ev

beginning of pregnancy 1/2/77 beginning of treat 7/2/77

end of treatment 19/2/77 delivery 2/3/77

A	n° Implants (A = G+H+F+E)	10	fetus weight,g	sex
B	n° fetuses (B = G+H+F)	10	37,4	M
			32,4	M
			42,1	M
C	n° alive	10	39,9	M
			37,7	F
D	n° dead	-	39,2	F
			35,7	F
E	n° reabsorptions	-	36,9	F
F	n° abortions	-	37,3	F
			39,3	F
G	n° male born	4		
H	n° female born	6		
I	n° corpus luteus rig	5		
L	n° corpus luteus-left	5		

Observations

time	animal weight,g	dietetic consumption
0	3050	
5	3170	162
10	3230	188
15	3310	154
20	3390	140
25	3500	168
30	3710	100

super-numerary ribs in 1 case

lack of 6th point of ossification in 1 case.

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Teratology n° 023

Esafosfina

rabbit n° 11 group II° treatment 100 mg/K ev.

beginning pregnancy 1/2/77 beginning treat. 7/2/77

end of treatment 9/2/99 delivery 2/3/77

A	n° Implants (A = G+H+F+E)	11	fetus weight, g	sex
B	n° fetuses (B = G+H+F)	11	29,2	M
			21,8	M
			33,4	M
C	n° alive	10	34,9	F
			27,9	F
D	n° dead	-	31,0	F
			32,4	F
E	n° reabsorptions	-	32,6	F
			30,9	F
F	n° abortions	1	25,2	F
G	n° male born	3		
H	n° female born	7		
I	n° corpus luteus right	6		
L	n° corpus luteus left	6		

Observations

supernumerary ribs in 1 cases

time	animal weight g	dietetic consumption
0	2590	
5	2670	180
10	2810	192
15	2980	190
20	2940	130
25	3000	180

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Teratology n° 023

rabbit n° 12 group II° treatment Esafosfina 100 mg/K ev

beginning of pregnancy 22/2/77 beginning of treat 28/2/77

end of treatment 12/3/77 delivery 23/3/77

A	n° Implants (A = G+H+F+E)	9	fetus weight,g	sex
B	n° fetuses (B = G+H+F)	9	31,0	M
			38,3	M
			37,4	M
C	n° alive	9	37,1	M
			30,9	F
D	n° dead	-	34,5	F
			27,1	F
E	n° reabsorptions	-	48,0	F
F	n° abortions	-	38,3	F
G	n° male born	4		
H	n° female born	5		
I	n° corpus luteus-rgh	5		
L	n° corpus luteus-left	4		

Observations

supernumerary ribs in 2 cases

time	animal weight g	dietetic consumtion
0	2920	
5	3000	120
10	3050	120
15	3120	130
20	3180	148
25	3350	170
30	3450	100

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Teratology n°...023 .....

rabbit n° ..1..... group ..III°..... treat. **Control** phys.sol.4ml/k iv

beginning pregnancy ..4/1/77.....beginning treat ...10/1/77.....

end of treatment ..29/1/77..... delivery ..2/2/77.....

A n° Implants
(A = G+H+F+E)

fetus weight,g sex

B n° fetuses
(B = G+H+F)

C n° alive

D n° dead

E n° reabsorptions

F n° abortions

G n° male born

H n° female born

I n° corpus luteus rgh

L n° corpus luteus left

Observations

Tempi	Peso animale ,g	Consumo dietetico ,g
0	2680	
5	2735	125
10	2950	136
15	2900	130
20	2650	80
25	3050	140

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Teratology n° 023 Control.

rabbit n° 2 froup III° treatment phys.sol 4ml/k iv

beginning pregnancy 4/1/77 beginning treat. 10/1/77

end of treatment 29/1/77 delivery 2/2/77

A	n° Implants (A = G+H+F+E)	6	fetus weight,g	sex
B	n° fetuses (B = G+H+F)	2	44,5 42,5	M F
C	n° alive	2		
D	n° dead	-		
E	n° reabsorptions	4		
F	n° abortions	-		
G	n° male born	1		
H	n° female born	1		
I	n° corpus luteus-right	3		
L	n° corpus luteus-left	5	Observations	

time	animal weight g	dietetic consumption
0	3350	
5	3440	115
10	3150	90
15	3430	140
20	3570	200

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Teratology n° 023

Control

rabbit n° 3 group III° treatment phys.sol.4,

beginning of pregnancy 4/1/77 beginning of treat. 10/1/77

end of treatment 29/1/77 delivery 2/2/77

A	n° Implants (A = G+H+I'+L)	9
B	n° fetuses (B = G+H+I')	9
C	n° alive	9
D	n° dead	-
E	n° reabsorptions	-
F	n° abortions	-
G	n° male born	4
H	n° female born	5
I	n° corpus luteus-right	5
L	n° corpus luteus-left	4

fetus weight,g	sex
29,0	M
40,0	M
33,9	M
31,7	M
24,0	F
32,8	F
30,6	F
25,5	F
28,8	F

Observations

time	animal weight	dietetic consumption
0	2880	
5	3040	125
10	3120	128
15	3290	142

lack of the 6th point of os cation in 4 cases.

Fetuses of reduced somatic in 2 cases.

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Teratology n° 023 .....

Control

rabbit n° 4 ..... group III° .....treatment phys.sol.

beginning of pregnancy 4/1/77 ..... beginning of treat 10/1/77..

end of treatment ...29/1/77..... delivery ..2/2/77.....

A	Implants (A = G+H+F+E)	7	fetus weight,g / sex
B	n° fetuses (B = G+H+F)	7	35,6 M 25,2 M 35,[illegible] M 32,0 F 31,1 F 36,2 F 36,1 F
C	n° alive	7	
D	n° dead	-	
E	n° reabsorptions	-	
F	n° abortions	-	
G	n° male born	3	
H	n° female born	4	
I	n° corpus luteus-right	4	
L	n° corpus luteus-left	3	

Observations

lack of the 6th point of os
fication in 1 case

time	animal weight g	dietetic consumption
0	3510	
5	3570	128
10	3550	140
15	3540	140
20	3670	138
25	3670	150

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Teratology n° 023

rabbit n° 5 group III° treat. phys. sol. 4ml/ Control

beginning of pregnancy 18/1/77 beginning of treat. 24/1/7

end of treatment 5/2/77 delivery 17/2/77

A	N° implants (A = G+H+F+E)	10	
B	N° fetuses (B = G+H+F)	10	
C	N° alive	10	
D	N° dead	-	
E	N° reabsorptions	-	
F	N° abortions	-	
G	N° male born	5	
H	N° female born	5	
I	N° corpus luteus-right	6	
L	N° corpus luteus-left	4	

fetus weight, g	sex
33,7	M
41,0	M
29,7	M
31,4	M
29,6	M
22,6	F
29,7	F
27,7	F
30,0	F
28,8	F

Observations

time	animal weight g	dietetic consumption
0	2640	
5	2780	166
10	2900	196
15	3350	200
20	3120	200
25	2950	200

supernumerary ribs in 1 ca
lack of the 6th point of o
fication in 1 case

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Teratology n° 023

rabbit n° 6 group III° treat. Control phys sol 4ml/k

beginning of pregnancy 1/2/77 beginning of treat. 7/2/77

end of treatment 19/2/77 delivery 2/3/77

A	N° fetuses (A = G+H+F+E)	13
B	N° fetuses (B = G+H+F)	13
C	N° alive	12
D	N° dead	-
E	N° reabsorptions	
F	N° abortions	1
G	N° male born	5
H	N° female born	7
I	N° corpus luteus-rg	7
L	N° corpus luteus-left	6

fetus weight,g	sex
21,2	M
26,3	M
28,4	M
26,1	M
26,2	M
27,8	F
25,5	F
31,0	F
26,9	F
35,5	F
25,9	F
26,7	F

Observations.

supernumerary ribs in 1 case

time	animal weight g	dietetic consumption
0	2825	
5	2900	148
10	2740	132
15	2830	200
20	3060	144
	3200	104

R. F.

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Teratology n° 023

rabbit n° 7 group III° treat Control phys sol 4ml/

beginning of pregnancy 1/2/77 beginning of treat 7/2/77

end of treatment 19/2/77 delivery 2/3/77

A	N° implants (A = G+H+F+E)	9
B	N° fetuses (B = G+H+F)	9
C	N° alive	9
D	N° dead	-
E	N° reabsorptions	-
F	N° abortions	-
G	N° male born	4
H	N° fEmale born	5
I	corpus luteus-right	5
L	corpus luteus-left	4

fetus -weight, g	sex
33,5	M
37,5	M
26,9	M
29,9	M
23,8	F
31,0	F
30,1	F
30,1	F
22,9	F

Observations

time	animal weight, g	dietetic consumption
0	2825	
5	2950	180
10	3100	196
15	3220	146
20	3330	196
25	3450	118

supernumerary ribs in 1 ca

lack of the 6th point of o
fication in 1 case

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Teratology n° 023

Control

rabbit n° 8 group III° treat phys sol 4ml/k

beginning of pregnancy 1/2/77 beginning of treat 7/2/77

beginning of treatment 19/2/77 delivery 2/3/77

A	N° fetuses (A = G+H+F+L)	4	fetus weight,g	sex
B	N° fetuses (B = G+H+F)	4	44,7	F
			43,6	F
			45,0	F
C	N° alive	4	41,3	M
D	N° dead	-		
E	N° reabsorptions	-		
F	N° abortions	-		
G	N°male born	1		
H	N°female born	3		
I	N°corpus luteus-right	3		
L	N°corpus luteus-left	1		

Observations

time	animal weightg	dietetic consumtion
0	3230	
5	3210	190
10	3430	200
15	3540	188
20	3620	118
25	3630	180

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Teratology n° 023

rabbit n° 9 group III° treat. phys sol Control 4ml/k

beginning of pregnancy 22/2/77 beginning of treat 28/2/77

end of treatment 12/3/77 delivery 23/3/77

A	N° Implants (A = G+H+F+L)	12
B	N° fetuses (B = G+H+F)	12
C	N° alive	11
D	N° dead	-
E	N° reabsorptions	-
F	N° abortions	1
G	N° male born	3
H	N° female born	8
I	N° corpus luteus-right	4
L	N° corpus luteus-left	7

fetus	weight,g	sex
	37,0	M
	39,9	M
	26,9	M
	28,7	F
	28,1	F
	38,0	F
	41;0	F
	30,4	F
	38,5	F
	38,2	F
	25,4	F

time	animal weight g	dietetic consumption
0	3120	
5	3200	146
10	3480	160
15	3560	200
20	3610	166
[illegible]	3665	150
[illegible]	3620	90

Observations

supernumerary ribs in 4 case

lack of the 6th point of ossification in 1 case

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Dr. Alfredo Nunziata

CRF consorzio ricerca farmaceutica

Teratology n° 023

Control

rabbit n° 10 group III° treat phys sol 4ml/k

beginning of pregnancy 22/2/77 beginning of treat 28/2/7

end of treatment 12/3/77 delivery 23/3/77

A	N° implants (A = G+H+F+E)	8	fetus weight,g	sex
B	N° fetuses (B = G+H+F)	8	42,6	M
			43,4	M
C	N° alive	8	35,3	M
			44,4	M
D	N° dead	-	36,5	M
			29,7	F
E	N° reabsorptions	-	40,0	F
			36,9	F
F	N° abortions	-		
G	N° male born	5		
H	N° female born	3		
I	N° corpus luteus-right	6		
L	N° corpus luteus-left	2		

Observations

time	animal weight g	dietetic consumtion
0	2740	
5	2800	100
10	2900	140
15 20	3020	180

supernumerary ribs in 2 cas

lack of the 6th point of os fication in 2 cases

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Teratology n° 023

rabbit n° 11 III° Control

beginning of pregnancy 22/2/77 beginning of treat. 28/2/77

end of treatment 12/3/77 delivery 23/3/77

A	N° implants (A = G+H+F+E)	11
B	N° fetuses (B = G+H+F)	11
C	N° alive	10
D	N° dead	-
E	N° reabsorptions	-
F	N° abortions	1
G	N° male born	3
H	N° female born	7
I	N°corpus luteus-right	7
L	N° corpus luteus-left	4

fetus weight,g	sex
35,4	M
47,1	M
49,4	M
37,6	F
29,3	F
49,1	F
36,3	F
26,7	F
36,9	F
39,6	F

Observations

supernumerary ribs in 3 cas

time	animal weight,g	dietetic consumpt,g
0	3070	
5	3200	150
10	3300	200
15	3400	190
20	3470	172
30	3600	100

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Teratology n° 023

rabbit n° 12 group III° treat.phys sol 4ml/k iv Control

beginning pregnancy 22/2/77 beginning treat 28/2/77

beginning of treat 12/3/77 delivery 23/3/77

A	N° implants (A = G+H+F+E)	8	
B	N° fetuses (B = G+H+F)	8	
C	n° alive	8	
D	n° dead	-	
E	n° reabsorptions	-	
F	n° abortions	-	
G	n° male born	4	
H	n° female born	4	
I	n° corpus luteus-right	4	
L	n° corpus luteus-left	4	

fetus weight,g	sex
45,2	M
52,6	M
39,7	M
36,3	M
42,2	F
45,5	F
42,5	F
45,1	F

Observations

time	animal weight g	dietetic consumt. g
0	3160	
5	3200	80
10	3250	170
15	3420	176
20	3610	168
25	3820	124
30	3830	110

supernumerary ribs in 1 case

lack of the 6th point of ossification in 2 cases

open bregma in 2 cases

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